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NANOCOCHLEATES: A NOVEL DRUG DELIVERY APPROACH

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ABSTRACT

An innovative drug delivery system called as nanocochleate allows the systemic and oral distribution of different charged drug molecules into a multilayered structure that contains a solid-lipid bilayer in the form of a sheet that has been rolled up spirally. The nanocochleate structure shields the enclosed molecules from the hostile environment. Drugs that are hydrophobic, positively charged, negatively charged, and have poor oral absorption can be encapsulated by nanocochleate. Creating nanocochleates and using them to deliver a wide range of active ingredients for various uses. Because nanocochleates have far fewer restrictions than conventional dosage forms and delivery systems, they are more effective. Expands in scope and promise as a medication delivery mechanism.

KEYWORDS: Nanocochleates, Bilayers, Phosphatidyl serine, Liposomes, Phospholipids.

INTRODUCTION

In order to possibly deliver drugs safely and effectively, the nanocochleate drug delivery vehicle is based on encapsulating drugs in multilayered, lipid crystal matrix. A sequence of lipid bilayers make up the spherical (cigar-like) microstructures known as nanocochleates.[1] The stable phospholipid-cation precipitates used as nanocochleate delivery vehicles are typically constituted of phosphatidylserine and calcium. They feature an unusual multilayered structure made up of solid lipid bilayer sheets that are stacked or spiral-rolled and have little to no interior aqueous space. For connected "encochleated" molecules, this structure offers protection from deterioration. Even though the outside layers of the nanocochleate may be exposed to severe environmental conditions or enzymes, the inside of the nanocochleate structure is made up of a succession of solid layers and components that are enclosed within

the structure and stay intact. Because nanocochleates have surfaces that are both hydrophobic and hydrophilic, they can be used to encapsulate both hydrophobic and hydrophilic drugs.[2]

Routes of administration of nanocochleate

Drugs can be delivered effectively orally thanks to nanocochleates drug delivery vehicles. Rectal, sublingual, nasal, subcutaneous, topical, parentral, transdermal, spinal, intra-arterial, bronchial, intrauterine, mucosal, intra articular, intra-vaginal, lymphatic and any other mucosal surfaces are examples of alternative routes of administration.[3]

Dosage forms available for nanocochleate drug delivery

1. Capsules, tablet, powders, solution, lozenges, pills, cachets or a suspension or an emulsion are all acceptable oral dosage forms.
2. Sprays, creams, gels, ointments, solutions, powders, pastes, lotions, patches and inhalants for external or transdermal application.
3. Sterile isotonic water or non-aqueous solutions, dispersions, suspensions, or emulsions for parenteral delivery, as well as sterile granules that can be turned into sterile injectable solutions or dispersions right before use.[4]

Advantages of nanocochleates

1. They have a lipid-bilayer matrix that acts as a carrier and is made of basic lipids that are non-toxic, non-immunogenic, and non-inflammatory and are found in animal and plant cell membranes.
2. They effectively incorporate biological molecules into the lipid-bilayer of the cochleate structure, especially those with hydrophobic groups.
3. They can be made quickly and securely.
4. Because the lipids in nanocochleates are less prone to degradation, they are more durable than liposomes. Unlike liposome molecules, which are dissolved by lyophilization, they retain their structure even after being lyophilized.
5. They increase a wide range of compounds' oral bioavailability, including those whose solubility in water is weak and protein and peptide biopharmaceuticals, which have historically been challenging to give. (e.g., ibuprofen for arthritis).
6. Instead of chemically interacting with the drugs, they entrap or protect the active ingredient within a crystal matrix.
7. They lessen the drug's poisonous stomach irritants and other adverse effects.

8. Rather than chemically interacting with the drugs, they entrap or encase the active ingredient inside a crystal matrix.
9. They safeguard the encochleated drugs from degradation by preventing contact to harmful environmental factors like direct sunlight, oxygen, water, and temperature.
10. They can be created as specific formulations with dosages and antigen concentrations that are preset.[5]

Limitations of nanocochleate drug delivery

1) Manufacturing is very expensive.
2) They need particular storing circumstances.
3) Aggregation can occasionally happen while being stored.[6]

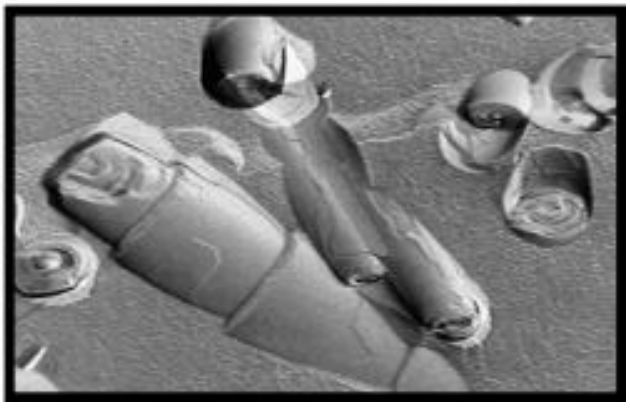

Figure 1: Nanocochleates.

Cochleate-cell interaction

Human fibroblast cells are incubated with nanometer-sized cochleates and liposomes that both contain a fluorescently labeled lipid component under identical conditions. Cells exposed to cochleate exhibit bright fluorescent cell surfaces, whereas those incubated with liposome can't exhibit bright fluorescent cell surfaces. This suggests that, in contrast to liposomes without an edge, cochleates edges can cause them to bond with cell surfaces. Tobramycin cochleates, which work by inhibiting intracellular ribosomes, can be used in bacterial activity assays to confirm this theory of cochleate fusion with cell membrane. According to several experts, tobramycin bridge cochleate in nanometer size exhibited better antimicrobial activity than the drug's solution.[7]

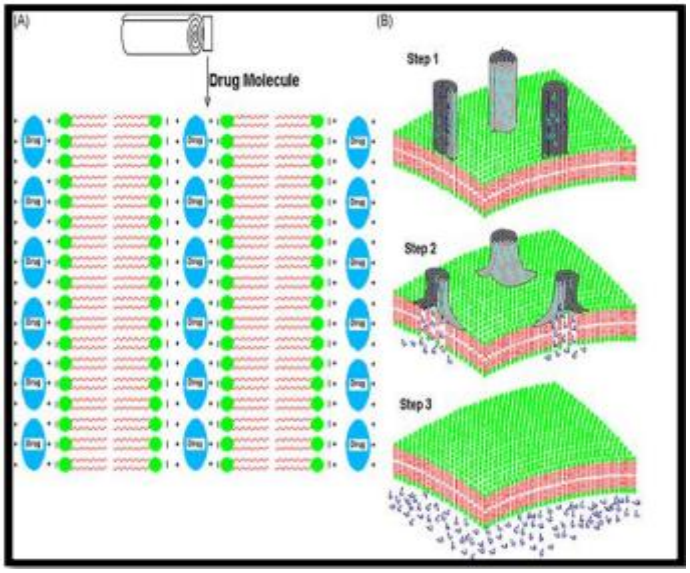

Figure 2: Cochleate-cell interaction.

Mechanism of nanocochleate drug delivery

Following oral delivery, the stomach is where nanocochleates are absorbed. Nanocochleates transport their payload molecule into blood vessels after crossing the digestive mucosa.[7]

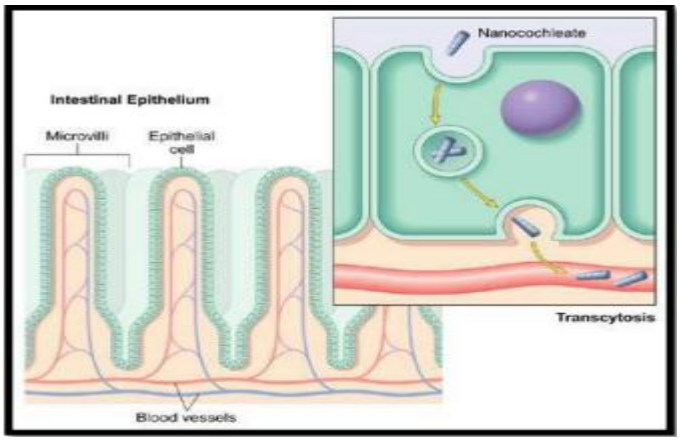

Figure 3: Nanocochleate absorption from intestine.

When administered via a different method than intravenous, they pass through the related cell and enter the circulatory system. They are then transported to the desired cell after entering circulation.[7]

Methods of formulation

Typically, the following techniques are used to make the nanocochleates

1. Hydrogel Method.
2. Trapping method.
3. Liposome before cochleates dialysis method.

4. Direct calcium dialysis method.
5. Binary aqueous- aqueous emulsion system.

Hydrogel method

Cochleate formation is a multi-step procedure. In the hydrogel technique, tiny, unilamellar liposomes containing the drug were first created and then added to polymer A, which can be phosphatidylserine, dextran, polyethylene glycol, etc. The second polymer, B (which could be polyvinylpyrrolidone, polyvinyl alcohol, Ficoll, polyvinyl methyl ether, etc.), was then added along with the mixture of the first two. The two plastics couldn't mix with one another. The polymers' immiscibility causes the creation of a watery two-phase system.

The addition of a cation salt solution to the two-phase system caused the cation to migrate into the second polymer and then into the particles made up of the polymer and liposomes, resulting in the cationic cross-linking of the polymers. enabling the development of tiny cochleates. The created cochleates were then rinsed to eliminate the polymer before being lyophilized or re-suspended in a physiological buffer or other suitable pharmaceutical carrier. In Fig. 4, the circuit layout is displayed.[8]

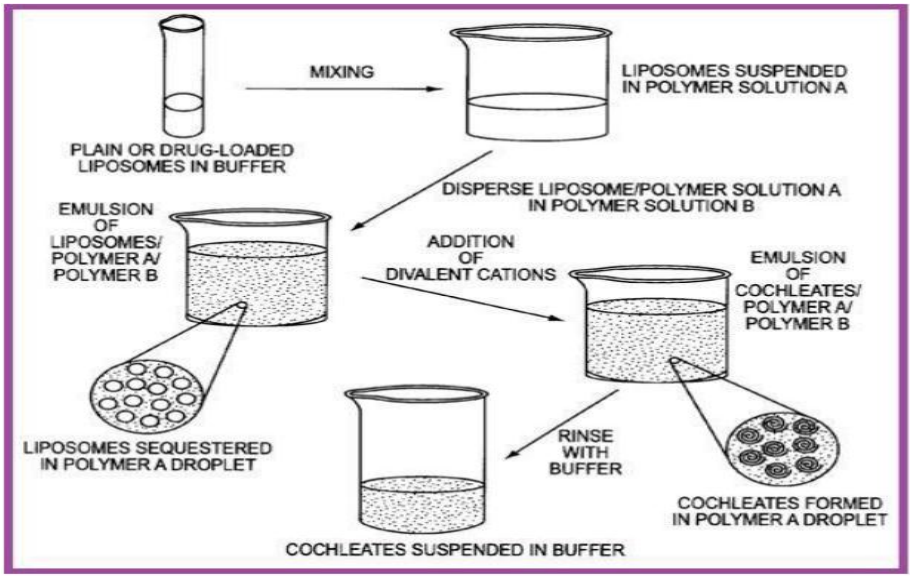

Figure 4: Hydrogel Method.

Trapping method

This procedure calls for the creation of phosphatidylserine liposomes, which are then added, drop by drop, a CaCl2 solution. Either adding water to phospholipid powder or introducing the water phase to a phospholipid layer can produce liposomes. In Fig. 5, the processing technique is presented schematically.[9]

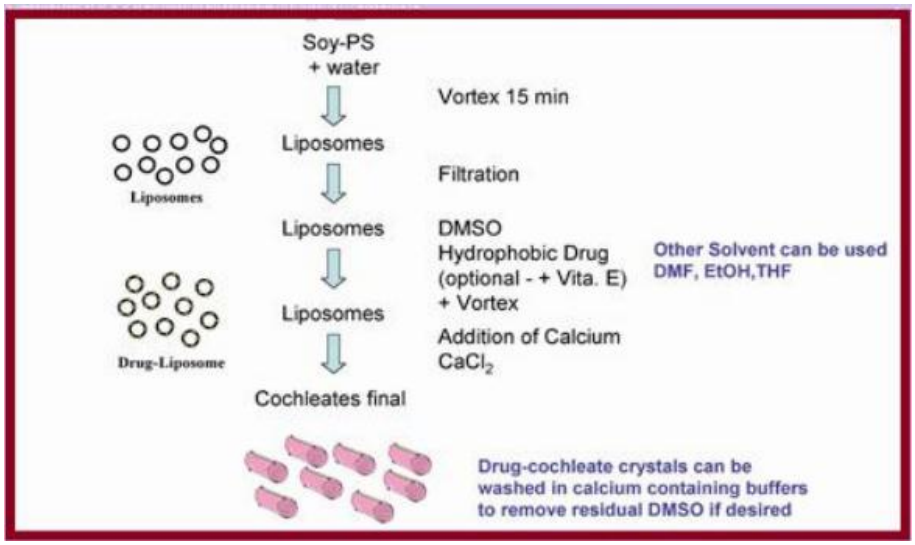

Figure 5: Schematic presentation of trapping method.

Liposome before cochleates dialysis method

In this procedure, a combination of lipid and detergent is used as the beginning substance, and double dialysis is used to remove the detergent. By dialyzing the combination first with buffer and then with calcium chloride solution, cochleates are formed. This technique is appropriate for encapsulating hydrophobic substances or drugs that contain hydrophobic regions like membrane proteins.[10]

Direct calcium dialysis method

In contrast to the LC technique, this process does not require the creation of intermediate liposomes, and the cochleates produced are large in size. The oil and detergent combination was dialyzed immediately against a calcium chloride solution. In this technique, bilayer condensation by calcium competes with detergent elimination from detergent/lipid/drug micelles to produce needle-shaped, three-dimensional structures. A predetermined quantity of polynucleotide was combined with a mixture of phosphatidylserine and cholesterol (9:1 wt. ratio) in extraction buffer and non-ionic surfactant, and the solution was vortexed for 5 minutes. The resulting clear, colorless solution was dialyzed at room temperature against three changes of buffer (at least four hours between each change). Although 3 mM Ca2+ is adequate and other concentrations might be compatible with cochleate formation, 6 mM Ca2+ is the ultimate dialysis that is typically used. For every modification, the dialysate to buffer ratio was at least 1:100. The whitish calcium-phospholipid precipitates that result have been given the name DC cochleates. The suspension includes numerous needle-like structures and numerous particulate structures with a width of up to several microns, as seen under light microscope.[11]

Binary aqueous-aqueous emulsion system

In this technique, either high pH or the film process is used to create tiny liposomes, which are then combined with a polymer, such as dextran. A second, non-miscible polymer is then infused with the dextran/liposome phase. (i.e., PEG). Following the addition of the calcium, which gently diffused from one phase to the next to create nanocochleates, the gel was washed away. The sublingual transport of injectable medicines was proven to be enhanced by the nanocochleates. The cochleates produced using this technique have particles smaller than 1000 nanometer.[12]

Characterization of nanocochleate

1) Determination of particle size distribution

Malvern 2000SM (Malvern, UK) is used in the laser diffraction method to determine the average particle size of distributed cochleates. Its measurement is carried out at a temperature of 302°C and an observation angle of 90°. The volume mean diameter D, which is the average diameter of a spheroid with a volume equal to that of the particle being measured, is used to describe the mean vesicle size.[13,14]

Structure and Morphology of the cochleates by Transmission Electron Microscopy (TEM)

Transmission electron microscopy (TEM) can be used to analyze the nanocochleate's shape. To create a thin liquid layer, a drop of diluted material is applied to a copper grid that has been coated with carbon. The material is then inspected and captured on camera using a Zeiss EM 109 transmission electron microscope at an accelerating voltage of 80 Kv.[15,16,17]

Drug content

At 25°C, the distributed nanocochleate suspension is centrifuged for 40 minutes at 15,000 rpm. The complimentary medicine After appropriate reduction, the concentration in the supernatant can be measured using a technique like UV-Vis spectrophotometry.[18,19]

Density

A gas pyrometer is used to determine the density of nanocochleate in air or helium. Due to the structure's unique surface area and permeability, the approximation obtained with air and helium is much clearer.[18]

Specific surface area

Using a sorptometer, the specific surface area of lyophilized nanocochleate is determined.

Formula: A = 6/ρd

A stands for specified surface area, ρ for density, and d for cochleate width. The measured and computed specified surface areas occasionally reasonably match up, but occasionally residual structure will cause a slight variation in the measured values.[18]

Surface charge determination

Nanocochleate's contact with the living surroundings and its electrostatic interactions with bioactive substances are determined by the type and strength of its surface charge. The particle motion in an electrical field can be evaluated to determine the surface charge. The speeds of nanocochleate are determined using laser diffractometry, such as velocimetry or laser doppler anemometry.[18]

Entrapment Efficiency (EE) of Nanocochleate

Cochleates are divided into 100 µl aliquots and placed in spinning containers. Each container receives 60 µl of pH 9.5 EDTA and 1 milliliter of ethanol while being vortexed. The final mixture is transparent and white. After properly diluting the samples, absorbance was measured to determine the entrapment effectiveness in accordance with formulae.[20,21]

Entrapment efficiency = Amount of API present in cochleates / Total amount of API

Cochleates cell interaction study

2% luminous lipid is combined with negatively charged lipids to create fluorescent cochleates, which are then used to study how cochleates interact with cell membranes. Cell surfaces turn fluorescent and can be seen under fluorescent microscopy when cochleates engage with the cell membrane through a fluorescent lipid transfer.[22] Cell surfaces become fluorescent when subjected to cochleates that are smaller than a nanometer, according to a research by Villa et al.[23]

Stability study

Cochleates dispersions can be kept at a range of 2 to 8 °C and 252 °C/60% RH for three months in order to conduct a stability research on them. The formulation's durability is assessed in terms of changes in entrapment efficiency (%EE) and cochleate particulate size.[21,24]

In-vitro drug release study

Diffusion cell method

Double chamber diffusion cells on a shake platform are typically used in the diffusion cell technique. Between the two compartments is maintained the Millipore low protein binding membrane. Phosphate solution is present in the receiver compartment, and the formulation is present in the donor chamber. Using traditional analytical techniques, the receptor region is tested for the released substance at various time periods.[25]

Applications of nanocochleate

1. Proteins, peptides, and DNA have all been delivered using nanocochleates in immunization and gene therapy uses.[26]
2. Nanocochleates can add Omega-3 fatty acids to biscuits, noodles, stews, cakes, muffins, and other foods without changing the flavor or aroma of the final product.[27]
3. Amphotericin B, a potential antifungal drug, may be delivered orally and parenterally using nanocochleates, which has a high safety profile and lower cost of care. The prepared cochleates of Amphotericin B shows better stability and effectiveness at low doses. They demonstrate enhanced patient cooperation.[28]
4. The benefit of cochleates would be a decrease in toxicity and an increase in antimicrobial action.[27]
5. Making an Apo-A1 formulation based on nanocochleate for treating atherosclerosis and other coronary heart diseases.[28]
6. Nanocochleates have the ability to stabilize and preserve an expanded spectrum of micronutrients and potential to increase the nutritional content of processed foods.[26]
7. The idea of "super foods" is now a reality thanks to nanocochleates, which can be used to deliver nutrients like vitamins, omega fatty acids that are more efficient to cells, and lycopene without changing the color or taste of food. These are anticipated to provide a variety of potential benefits, including increased energy, improved cognitive functions, better immune function, and antiaging benefits.[15]

CONCLUSION

Due to its distinctive multilayered structure, nanocochleate safeguards active substances or chemicals that are being transported. It keeps encochleated molecules from coming into touch with the harsh atmosphere. Due to their advantages over other drug delivery methods, nanocochleates are now frequently used to transport a variety of therapeutically active

substances. Consequently, the creation of nanocochleate drug delivery systems is becoming more significant in the pharmaceutical industry in order to transfer suitable and desirable drug molecules into the body with high potential.